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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/800,016	03/05/2001	Dean K. Pettit	3253	5188

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/800,016	PETTIT ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9-13,16 and 18-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,9-13,16 and 18-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/28/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/28/2007 has been entered.

Claims 1, 3-7, 9-13 and 16, 18-24 and newly introduced claim 25 are pending and under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-7, 20-21 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. There is no basis in the specification as originally filed for a solution comprising 250 ug/mL of GM-CSF. Applicants point to page 5, lines 12-14 for basis for the limitation; however, the paragraph at that location merely reads:

In one preferred embodiment of the subject invention, sargramostim is formulated as described above for LEUKINE® Liquid except that EDTA is added to a concentration of 5 mM. In another preferred embodiment, sargramostim is formulated as described above for LEUKINE® Lyophilized, except that 5 mM EDTA is added to the solution prior

to lyophilization. Alternatively, dry EDTA powder in appropriate amounts may be mixed with the lyophilized LEUKINE® before it is packaged.

Rejections Over Prior Art

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-7, 9-13 and 16, 18-24 remain and newly introduced claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over the LEUKINE® Sargramostim product insert, cited by applicants in paper number 5, in view of U.S. Patent Number 5,217,954 (Foster et al.) and U.S. Patent Number 6,620,784 (Ferrara et al.), and in the case of claims 4-8, further in view of U.S. Patent Number 5,545,536 (Kaushansky et al.) for reasons of record in the Office Action mailed 2/23/2005. Applicants arguments filed 3/28/2007 have been fully considered but are not deemed persuasive.

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949). A showing of unexpected results must be based on evidence, not argument or speculation. In re Mayne, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997) (conclusory statements that claimed compound possesses unusually low immune response or unexpected biological activity that is unsupported by comparative data held insufficient to overcome prima facie case of obviousness).

The declaration by Dr. Baumann under 37 CFR 1.132 filed 3/28/2007 is insufficient to overcome the rejection of claims 1-7, 9 and 16-24 as set forth above because:

The nature of the fact to be established is that a preparation of GM-CSF comprising from 0.1mM to 50 mM EDTA shows an unexpected result, namely a unique pharmacokinetic profile, as characterized by declarant. Although, as shown in Exhibit 2, the tested preparation of GM-CSF had a different pharmacokinetic profile from the control, such is not sufficient to establish unexpected results for the claimed subject matter for the following reasons:

- The experiments described in the declaration do not compare the prior art composition with that which is claimed. As stated in the rejection set forth on 5/15/2003, "The Leukine® patient insert teaches that sargramostim is provided in liquid form at a concentration of 500 mcg/mL (micrograms per milliliter), with 1.1% benzyl alcohol, 40 mg/mL mannitol, 10 mg/mL sucrose, and 1.2 mg/mL tromethamine (third paragraph of insert). " The instant declaration states:

  The pharmacokinetic profiles of three sargramostim formulations after single subcutaneous administration in Cynomolgus monkeys were compared. The three sargramostim formulations are as follows; (

1) liquid formulation with EDTA and benzyl alcohol:
500 ug/ml sargramostim, 5.5 mM EDTA, 1.15% benzyl alcohol, 40 mg/ml mannitol, 10 mg/ml sucrose, and 10 mM Tris-HCI (pH 6.7 to 7.7);
(2) lyophilized material dissolved in benzyl alcohol but without EDTA:
500 ug/ml sargramostim, 0.9% benzyl alcohol, 40 mg/ml mannitol *or* 10 mg/ml sucrose, and 10 mM Tris-HCI, pH 6.15; and
(3) liquid formulation without EDTA or benzyl alcohol:
500 ug/ml sargramostim and 100 mM Tris-HCI, pH 7.4" (emphasis added).

Thus, the formulations declarant compares differ not only in the presence or absence of EDTA, but the first two formulations have different amounts of benzyl alcohol, mannitol or sucrose and different pH's. The pH's of the different formulae are 6.7-7.7, which is a one-log range, 6.15 and 7.4, respectively. Note that the exact pH of the first formulation is unknown, and that of the second formulation does not fall within the range for the first formulation. Finally, none of the formulations comprise the same composition as the prior art Leukine®, which additionally contains tromethamine. Thus, there are numerous variables in play other than the presence or absence of EDTA. As stated in the last Office Action, the appropriate comparison would have been between two aqueous preparations that differ only with respect to the presence or absence of EDTA.

- Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) and MPEP § 716.02(d) - § 716.02(e).

  The only tested concentration of EDTA was 5.5 mM. Even *if* the results therein were persuasive of an unexpected result, it would not be commensurate in scope with the claims, which include a range of 0.5 to 10 mM, a fifty- fold range. A single example is insufficient to enable a 50-fold range.
- Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (differences in sedative and anticholinergic effects

between prior art and claimed antidepressants were not unexpected). In In re Waymouth, 499 F.2d 1273, 1276, 182 USPQ 290, 293 (CCPA 1974), the court held that unexpected results for a claimed range as compared with the range disclosed in the prior art had been shown by a demonstration of "a marked improvement, over the results achieved under other ratios, as to be classified as a difference in kind, rather than one of degree." See MPEP 716.02.

The evidence relied upon should establish "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance." Ex parte Gelles, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992) (Mere conclusions in appellants' brief that the claimed polymer had an unexpectedly increased impact strength "are not entitled to the weight of conclusions accompanying the evidence, either in the specification or in a declaration."); Ex parte C, 27 USPQ2d 1492 (Bd. Pat. App. & Inter. 1992) (Applicant alleged unexpected results with regard to the claimed soybean plant, however there was no basis for judging the practical significance of data with regard to maturity date, flowering date, flower color, or height of the plant.). See also In re Nolan, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977) and In re Eli Lilly, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) as discussed in MPEP §716.02(c). See MPEP 716.02(b).

In this case, the difference between the formulations is minimal; looking at Exhibit 2, the Examiner notes that preparations 1 and 2 achieve relatively the same peak concentration, and the curves are within one standard deviation of each other for the entirety of the experiment, spanning 24 hours. The only possible difference is the biphasic nature of the curve for Sargramostim EDTA. However, this difference is minor; at best, it indicates that the patient would get a transient but immediate concentration spike; at one hour, the concentrations are virtually identical. Further, it is noted that the "mean liquid form w/o EDTA/benzyl alc. Actually maintains a higher effective concentrationfor a longer period of time as compared to formulation 1, above. Given that the error bars on Exhibit 2 are large, it is very difficult to conclude that any difference is real. Further, even if the difference is real, it does not appear to constitute "a marked improvement". Neither the specification nor the declaration points out why the observed result would constitute a marked improvement; the Examiner is not aware of

any situation in which accelerating the peak effective concentration of GM-CSF by a single hour would be considered to be a marked improvement, or of statistical and practical significance. In fact, even the declarant merely states that "the double-peak absorption profile is unique to the sargramostim formulation with EDTA after subcutaneous administration." The declarant does not state that this double peak is of any clinical significance, nor that it is an unexpected result. The Examiner maintains that "different" does not equate to an unexpected result of the sort that would overcome a *prima facie* finding of obviousness. It remains that the pertinent comparison has still not been presented, that the art teaches the addition of EDTA as a chelator to formulations of cytokines is known and routine, that one would expect different formulations to have different properties, but that merely being different does not constitute an unexpected result, that neither declarant nor the art of record has established that the observed biphasic curve is unexpected and unobvious and of both statistical and practical significance, and that the significance of the difference between the tested formulations is questionable, both because of the large standard deviations that indicate the results likely not to be of statistical significance, and because of the fleeting nature of the difference. Accordingly, the Baumann declaration is not sufficient to overcome the rejection.

Turning to the arguments filed 3/18/2007, applicants assert at page 7 that it is "unlikely that the differences between the compositions used in the experiments described in Dr. Scholz's Declaration and the prior art composition determine the presence or absence of the unique double-peak absorption profile of GM-CSF formulations." This argument has been fully considered but is not deemed persuasive because it is not supported by fact or evidence, nor is it stated in the declaration itself. The argument appears to be the opinion of the attorney. The case law as cited above is very clear that The evidence relied upon should establish "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance", and that any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. Whether the cause of the difference is likely or unlikely is an issue of lesser importance than the issue that the results themselves do not support a finding of unexpected results, nor does declarant assert that they do. Also at page 7,

"Applicants submit that as indicated in Dr. Baumann's Declaration, it is unlikely that reconstitution of lyophilized sargramostim contributes to the lack of the double-peak absorption profile in the formulation that does not contain EDTA." This argument has been fully considered but is not deemed persuasive because Dr. Baumann makes no such statement. Further note that the difference between lyophilized sargamostim and the liquid forms exceeds any difference between the liquid forms themselves. At page 8, applicant further asserts that it is "unlikely that the minor difference in benzyl alcohol concentration contributes to the lack of the double-pead absorption profile...". This argument has been fully considered but is not deemed persuasive because (a) the Examiner does not find that the double peak itself constitutes an unexpected or significant result as required, and (b) the argument is mere conjecture, addressing point not addressed by declarant, nor supported by fact or evidence. Finally, at pages 8-9, applicant asserts that the double-peak profile "is unique to GM-CSF formulations that contain EDTA and provides unexpected advantages." Once again, this argument has been fully considered but is not deemed persuasive because neither declarants nor the art have established that merely obtaining such a double peak is either unexpected or of practical significance. GM-CSF is a cytokine that supports "survival, clonal expansion, and differentiation of hematopoietic progenitor cells" (Leukine insert at page 1). The insert goes on to list as indications: use following induction chemotherapy in acute myelogenous leukemia, use in mobilization and following transplantation of autologous peripheral blood progenitor cells, use in myeloid reconstitution after autologous bone marrow transplantation, after allogenic bone marrow transplantation, or in bone marrow transplantation failure or engraftment delay. There is no evidence, nor does logic indicate, that achieving a biphasic profile as asserted by applicants would be of any significance for any of these indications. It remains that, with *both* declarations submitted under 37 C.F.R. §1. 132 that the peak effective concentration is the same regardless of the presence of EDTA, and that any differences in pharmacological profile are fleeting, occurring only in the first hour or so after treatment. The formulation *without* EDTA actually maintains peak concentration for a longer period of time, and all three curves in the Baumann declaration are identical from three hours onward. The Examiner allows that if one were treating an acute condition, such as sepsis, stroke or heart attack, that achieving an early peak concentration could have a significant effect on the outcome. However, the differences asserted

by applicant and declarants are simply of no significance when treating the indications listed in the Leukine insert.

It is believed that all pertinent arguments have been addressed.

Claims 10-13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over the LEUKINE® Sargramostim product insert, cited by applicants in paper number 5, in view of U.S. Patent Number 6,620,784 (Ferrara et al.) , and U.S. Patent Number 5,217,954 (Foster et al.), as cited in the rejection of claims 1-7, 9 and 16-24 above, and further in view of U.S. Patent Number 6,500,418 B1 (Dieckgraefe et al.) for reasons of record in the previous Office Action. Applicants arguments filed 7/11/2006 have been fully considered but are not deemed persuasive for reasons cited above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Gary Nickol, at telephone number 571-272-0835.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner

6/8/2007